
Using iPSC-derived neurons to uncover cellular phenotypes associated with Timothy syndrome.

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Public Summary:

Timothy syndrome is caused by a missense mutation in the L-type calcium channel Ca(v)1.2 that is associated with developmental delay and autism. We generated cortical neuronal precursor cells and neurons from induced pluripotent stem cells derived from individuals with Timothy syndrome. We found that cells from these individuals have defects in calcium signaling, activity-dependent gene expression, and differentiation. These findings provide strong evidence that Ca(v)1.2 regulates the differentiation of cortical neurons in humans and offer new insights into the causes of autism in individuals with Timothy syndrome.

Scientific Abstract:

Monogenic neurodevelopmental disorders provide key insights into the pathogenesis of disease and help us understand how specific genes control the development of the human brain. Timothy syndrome is caused by a missense mutation in the L-type calcium channel Ca(v)1.2 that is associated with developmental delay and autism. We generated cortical neuronal precursor cells and neurons from induced pluripotent stem cells derived from individuals with Timothy syndrome. Cells from these individuals have defects in calcium (Ca(2+)) signaling and activity-dependent gene expression. They also show abnormalities in differentiation, including decreased expression of genes that are expressed in lower cortical layers and in callosal projection neurons. In addition, neurons derived from individuals with Timothy syndrome show abnormal expression of tyrosine hydroxylase and increased production of norepinephrine and dopamine. This phenotype can be reversed by treatment with roscovitine, a cyclin-dependent kinase inhibitor and atypical L-type-channel blocker. These findings provide strong evidence that Ca(v)1.2 regulates the differentiation of cortical neurons in humans and offer new insights into the causes of autism in individuals with Timothy syndrome.

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